PATENT SPECIFICATION

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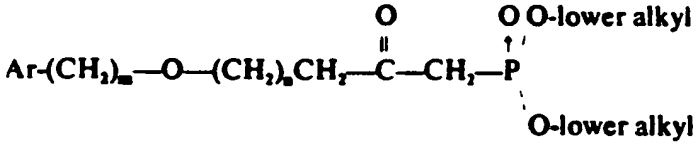
(19)

(54) SUBSTITUTED DIALKYL 2-OXOPROPYLPHOSPHONATES

(71) We, PFIZER INC, a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to intermediates useful in the preparation of certain novel analogs of the naturally occurring prostaglandins. In particular it relates to intermediates useful in the preparation of novel prostaglandins which are described and claimed in Patent Application 51758/73 (Serial No. 1,456,512).

The present invention provides a substituted dialkyl 2-oxopropyl phosphonate of the formula:



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wherein Ar is phenyl; 3,4-dimethoxyphenyl; 3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; α- or β-naphthyl or mono-substituted phenyl wherein said substituent is halogen, trifluoromethyl, phenyl, lower alkyl or lower alkoxy; and n and m are each integers from 0 to 3 with the proviso that the sum of n and m does not exceed 3, and lower indicates a group of 1—6 carbon atoms.

The invention also provides a process for preparing a compound of the formula I, which comprises reacting a lower alkyl ester of the formula:

wherein Ar, m and n are as defined above, with a dialkyl methylphosphonate of the formula:

The starting materials for the various novel compounds of this invention are available commercially or are made by methods well known to those skilled in the art. For example, to make dimethyl 2-oxo-3-phenoxypropylphosphonate, the starting material for the synthesis of the 16-phenoxy-17,18,19,20-tetranorprostaglandins, one cools a solution of dimethyl methylphosphonate in tetrahydrofuran to -78°C. in a dry nitrogen atmosphere and then adds *n*-butyl-lithium in hexane dropwise, slowly. After stirring methyl 2-phenoxyacetate is added dropwise. After 3 to 4 hours at -78°C. the reaction mixture is warmed to ambient temperature, neutralized with acetic acid and rotary evaporated to a white gel. The gelatinous material is taken up in water, the aqueous phase is extracted in

chloroform and the combined organic extracts are backwashed, dried, and concentrated to give the desired product.

To make substituted 16-phenoxy-17,18,19,20-prostaglandins, one requires substituted phenoxyacetic acids which are prepared by condensation of an appropriate phenol with a haloacetic acid or ester in the presence of base as described by J. M. Petersen, *Acta. Chem. Scandinavica, 5*, 519 (1951) or M. Beroza, *Agri. Food Chem., 4*, 49 (1956). Thus condensation of methyl bromoacetate with sesamol in the presence of sodium methoxide gives the 3,4-methylenedioxyphenoxyacetic acid methyl ester. Similarly, one may prepare *p*-chlorophenoxyacetic acid, 3,4,5-trimethoxyphenoxyacetic acid and *p*-phenylphenoxyacetic acid.

These acids are converted to esters by the usual method and thence into phosphonates as described above for the unsubstituted 16-phenoxy starting compound.

To make the starting material for the 16-phenyl-17,18,19,20-tetranorpropoxy prostaglandins, one requires the 2-(3-phenylpropoxy)acetic acid. This is prepared by method of Rothstein, *Bull. Soc. Chim., 51*, 691 (1932), converted to the ester and thence to the phosphonate as described for the 16-phenoxy compound.

To prepare the 16-benzyloxy-17,18,19,20-tetranorprostaglandins, one requires 2-benzyloxyacetic acid which is prepared by the method of H. Fisher and B. Gohlke, *Helv. Chim. Acta. 16*, 1130 (1933) and converted to the ester by standard methods and thence to phosphonate by the method described for 16-phenoxy compound.

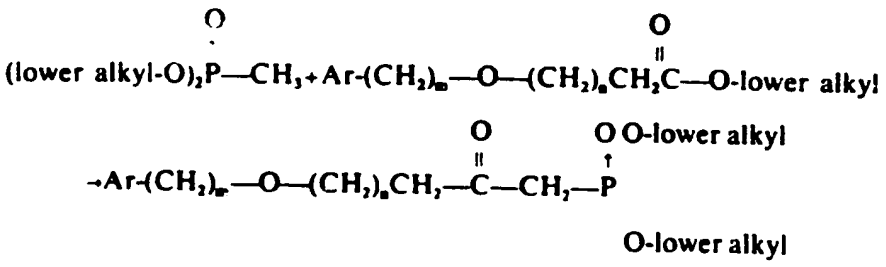
When 16-phenethoxy-17,18,19,20-tetranorprostaglandins are desired, one makes 2-(phenethoxy)acetic acid by, for example, the method of Rothstein, *Bull. Soc. Chim., 51*, 691 (1932), converts it to the ester and thence to the phosphonate as described for the 16-phenoxy compound.

To prepare the 17-phenoxy-18,19,20-trisnorprostaglandins, 3-phenoxypropionic acid is converted to the ester and thence to the phosphonate as for the 16-phenoxy compound.

To prepare 18-phenoxy-19,20-bisnorprostaglandins, 4-phenoxybutyronitrile is refluxed with 10% aqueous methanolic HCl to convert it to the 4-phenoxybutyric acid suitable for conversion to phosphonate as described for the 16-phenoxy case.

To prepare the 19-phenoxy-20-norprostaglandins, 5-phenoxyvaleric acid is prepared by the method of A. S. Carter, J. Am. Chem. Soc., *50* 1967 (1928) and converted to the phosphonate as described for the 16-phenoxy case.

SCHEME A.



As shown in Scheme A, the condensation of the appropriate ester with a dialkyl methylphosphonate produces the oxophosphonate. The esters are obtained as previously described.

The following non-limiting Example illustrates the invention. In this Example it will be appreciated that all temperatures are expressed in Centigrade, and boiling points are uncorrected.

EXAMPLE.

Dimethyl 2-Oxo-3-phenoxypropylphosphonate.

A solution of 33.2 g. (268 mmoles) dimethyl methylphosphonate (Aldrich) in 360 ml. dry tetrahydrofuran was cooled to −78° in a dry nitrogen atmosphere. To the stirred phosphonate solution was added 118 ml. of 2.34*M* *n*-butyl-lithium in hexane solution (Alfa Inorganics, Inc.) dropwise over a period of 18 minutes at such a rate that the reaction temperature never rose above −65°. After an additional 5 minutes stirring at −78°, 22.2 g. (134 mmole) methyl 2-phenoxyacetate was added dropwise at a rate that kept the reaction temperature less than

-70° (20 minutes). After 3.5 hours at −78° the reaction mixture was allowed to warm to ambient temperature, neutralized with 14 ml. acetic acid and rotary evaporated to a white gel. The gelatinous material was taken up in 175 ml. water, the aqueous phase extracted with 100 ml. portions of chloroform (3x), the combined organic extracts were backwashed (50 cc. H_2O), dried ($MgSO_4$), and concentrated (water aspirator) to a crude residue and distilled, b.p. 172—175° (0.5 mm) to give 24.6 g. dimethyl 2-oxo-3-phenoxypropylphosphonate.

The nmr spectrum ($CDCl_3$) showed a doublet centered at 3.75δ (J=11.5 cps, 6H) for

$$(CH_3O)—\overset{\overset{O}{\|}}{P}—,$$

a singlet at 4.7δ (2H) for $C_6H_5O—CH_2—CO—$, a doublet centered at 3.24δ (J=23 cps, 2H)

$$—\overset{\overset{O}{\|}}{C}—CH_2—P—,$$

and a multiplet at 6.8—7.5δ (5H) for the aromatic protons.

WHAT WE CLAIM IS:—

1. A compound of the formula:—

$$Ar\text{-}(CH_2)_m—O—(CH_2)_nCH_2—\overset{\overset{O}{\|}}{C}—CH_2—\overset{\overset{O\text{ O-lower alkyl}}{\uparrow}}{P}$$

$$\text{O-lower alkyl} \qquad \text{....I}$$

wherein Ar is phenyl; 3,4-dimethoxyphenyl; 3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; α- or β-naphthyl or monosubstituted phenyl wherein said substituent is halogen, trifluoromethyl, phenyl, lower alkyl or lower alkoxy; and n and m are each 0 or integers from 1 to 3 with the proviso that the sum of n and m does not exceed 3, and wherein "lower" indicates a group of 1—6 carbon atoms.

2. Dimethyl 2-oxo-3-phenoxypropylphosphonate.

3. A process for preparing a compound of formula I as claimed in claim 1, which comprises reacting a lower alkyl ester of the formula

$$Ar\text{-}(CH_2)_m—O—(CH_2)_nCH_2\overset{\overset{O}{\|}}{C}—O\text{-lower alkyl}$$

wherein Ar, m and n are as defined in claim 1, with a dialkyl methylphosphonate of the formula:

$$(\text{lower alkyl-O})_2\overset{\overset{O}{\uparrow}}{P}—CH_3$$

4. A process for preparing a compound of formula I as claimed in claim 1, substantially as hereinbefore described with reference to the Example.

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